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(54) Tetrahydro-Benzthiazoles, the Preparation Thereof and  
Their Use as Intermediate Products or as  
Pharmaceuticals

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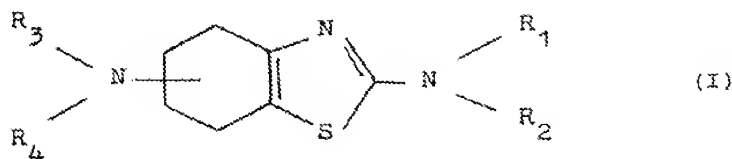
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Abstract

This invention relates to Compounds of general formula I



[wherein

$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

$R_2$  represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms), and  $R_4$  represents a hydrogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino

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or morpholino group] and acid addition salts thereof.

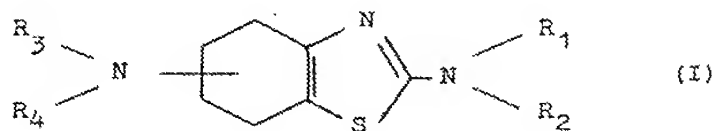
The compounds of general formula I above in which one of the groups  $R_1$  or  $R_3$  or both groups  $R_1$  and  $R_3$  represent an acyl group are useful intermediate products for preparing the other compounds of general formula I which have interesting pharmacological properties, particularly an effect on the central nervous system and/or the circulation.

The new compounds may be prepared using methods known per se.

Chemical Compounds

The present invention relates to tetrahydro-benzthiazoles, to processes for their preparation and to pharmaceutical compositions containing them.

- 5 According to one feature of the present invention, there are provided compounds of general formula I



[wherein

- 10  $R_1$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which  
15 the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

$R_2$  represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

- 20  $R_3$  represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms or represents a phenylalkyl or phenylalkanoyl group each containing  
25 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms) and  $R_4$  represents



a hydrogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino,  
 5 piperidino, hexamethyleneimino or morpholino group] and acid addition salts thereof.

Where the compound of formula I is a compound possessing a chiral centre, the invention extends to all possible isomers of the compound in question.

10 It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable acid addition salts, but other acid addition salts may find use, for example in the preparation of compounds of general formula I and  
 15 physiologically acceptable acid addition salts thereof. The expression "acid addition salts" as used herein includes salts formed with inorganic or organic acids.

The compounds of general formula I possess  
 20 interesting pharmacological properties, and in general show an effect on the central nervous system and/or the circulation.

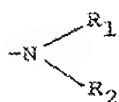
If in general formula I one of the groups  $R_1$  and  $R_3$  represents an acyl group or both of  $R_1$  and  
 25  $R_3$  represent acyl groups, these compounds of general formula I are valuable intermediate products for preparing other compounds of general formula I.

Preferred compounds of general formula I above are those wherein the group

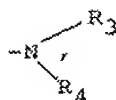


is in the 5 or 6-position.

As examples of the definitions of the groups

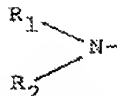


and



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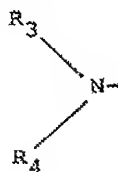
the



group may represent an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-isopropylamino, allylamino, buten-2-ylamino, hexen-2-ylamino, N-methyl-allylamino, N-ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-allylamino, propargylamino, N-methyl-propargylamino, N-n-propyl-propargylamino, formylamino, acetylamino, propionylamino, butanoylamino, hexanoylamino, N-methyl-acetylamino, N-allyl-acetylamino, N-propargyl-acetylamino, benzylamino, N-methyl-benzylamino, 2-chloro-benzylamino, 4-chloro-benzylamino, 4-fluoro-benzylamino, 3,4-dichloro-benzylamino, 1-phenylethylamino, 2-phenylethylamino, 3-phenyl-n-propylamino, benzoylamino phenacetilamino or 2-phenylpropionylamino group; and

25

the

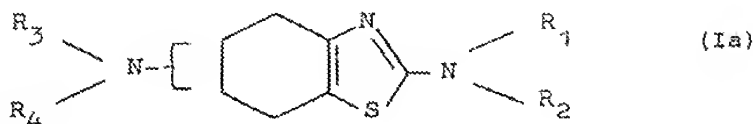


group may represent an amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, isobutylamino, tert.butylamino, n-pentylamino, isoamylamino, n-hexylamino, n-heptylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, methyl-ethylamino,

30

- methyl-n-propylamino, methyl-isopropylamino, ethyl-  
 isopropylamino, allylamino, buten-2-ylamino, hexen-  
 2-ylamino, diallylamino, N-methyl-allylamino, N-  
 ethyl-allylamino, N-n-propyl-allylamino, N-n-butyl-  
 5 allylamino, propargylamino, butin-2-ylamino, hexin-  
 2-ylamino, dipropargylamino, N-methyl-propargylamino,  
 N-ethyl-propargylamino, cyclopropylamino, cyclobutylamino,  
 cyclopentylamino, cyclohexylamino, cycloheptylamino,  
 N-methyl cyclohexylamino, N-ethyl-cyclohexylamino,  
 10 formylamino, acetylamino, propionylamino, butanoylamino,  
 pentanoylamino, hexanoylamino, heptanoylamino,  
 N-methyl-acetylamino, N-ethyl-acetylamino, N-n-  
 propyl-acetylamino, N-allyl-acetylamino, benzoylamino,  
 fluorobenzoylamino, chlorobenzoylamino, bromobenzoylamino,  
 15 phenylacetamino, 2-phenylpropionylamino, N-methyl-  
 benzoylamino, N-ethyl-chlorobenzoylamino, Dichlorobenzoyl-  
 amino, N-cyclohexyl-acetylamino, benzylamino, chloro-  
 benzylamino, bromobenzylamino, 1-phenylethylamino,  
 2-phenylethylamino, 2-phenyl-n-propylamino, 3-phenyl-  
 20 n-propylamino, N-methyl-benzylamino, N-ethyl-benzylamino,  
 N-ethyl-chlorobenzylamino, N-ethyl-2-phenylethylamino,  
 N-acetyl-benzylamino, N-acetyl-chlorobenzylamino,  
 N-allyl-benzylamino, N-allyl-chlorobenzylamino,  
 pyrrolidino, piperidino, hexamethyleneimino or  
 25 morpholino group.

Particularly preferred compounds of general  
 formula I are, however, the compounds of general  
 formula Ia



(wherein

$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichloro-  
5 benzyl or phenylethyl group;

$R_2$  represents a hydrogen atom or a methyl or ethyl group; and

$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms or an allyl, propargyl,  
10 benzyl, chlorobenzyl, phenylethyl, cyclopentyl or cyclohexyl group and  $R_4$  represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl group; or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino,  
15 piperidino, hexamethyleneimino or morpholino group) and especially the compounds wherein the group

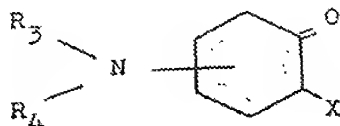


20 is in the 6-position, and acid addition salts thereof.

The new compounds may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

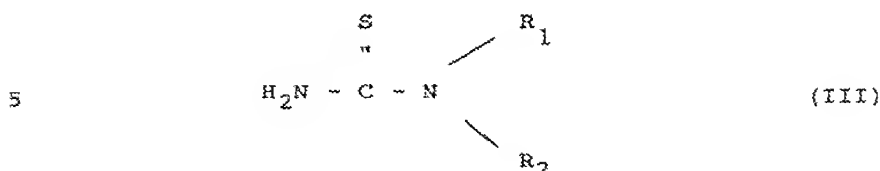
a) Reaction of a cyclohexanone of general formula II

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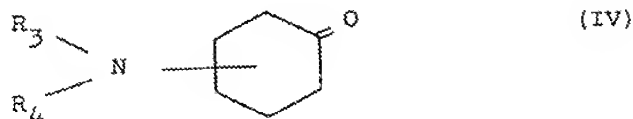
[wherein  $R_3$  and  $R_4$  are as hereinbefore defined; and X represents a nucleophilic leaving group such as a halogen atom (e.g. a chlorine or bromine atom)] with a thiourea of general formula III



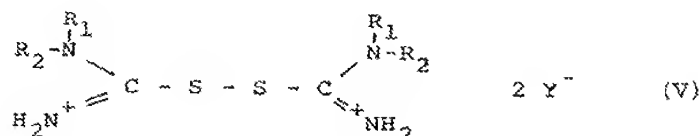
(wherein  $R_1$  and  $R_2$  are as hereinbefore defined).

The reaction is carried out in the melt or in the presence of a solvent or mixture of solvents (such as, for example, water, ethanol, water/ethanol, pyridine, dioxan, dioxan/water, glacial acetic acid, tetrahydrofuran or dimethylformamide) conveniently at temperatures of between 0 and 150°C, but preferably at temperatures of between 20 and 100°C, and optionally in the presence of a base (e.g. sodium hydroxide solution, sodium acetate, pyridine, triethylamine or N-ethyl-diisopropylamine). The compounds of general formula II used as starting materials need not be isolated.

20 b) Reaction of a compound of general formula IV



(wherein  $R_3$  and  $R_4$  are as hereinbefore defined) with a formamidine disulphide of general formula V



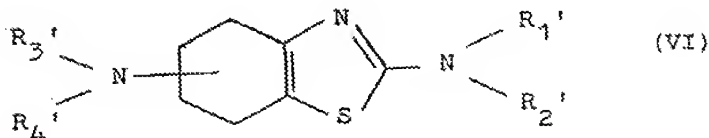
- 5 (wherein  $R_1$  and  $R_2$  are as hereinbefore defined; and  $Y^-$  represents an anion of an inorganic or organic acid).

The reaction is preferably carried out in  
 10 the melt or in the presence of a high-boiling solvent (such as, for example, glycol, dimethylformamide, diphenylether or dichlorobenzene) conveniently at temperatures of between 25 and 200°C, but preferably at temperatures of between 70 and 150°C.

- 15 c) For the preparation of compounds of general formula I wherein at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents a hydrogen atom:

cleavage of a protecting group from a compound of general formula VI

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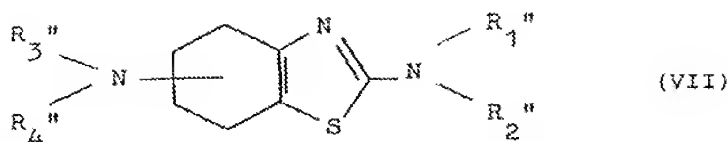


[wherein at least one of the groups  $R_1'$ ,  $R_2'$ ,  $R_3'$  or  $R_4'$  represent a protecting group for an amino group such as, for example, an acyl or alkoxycarbonyl group (e.g. an acetyl, propionyl, methoxycarbonyl or ethoxycarbonyl group) or  $R_1'$  and  $R_2'$  or  $R_3'$  and  $R_4'$  together with the nitrogen atom between them represent an imido group (e.g. a phthalimido group); and the remaining groups  $R_1'$ ,  $R_2'$ ,  $R_3'$  and  $R_4'$  have, other than the acyl groups, the meanings given for  $R_1$  to  $R_4$  hereinbefore].

The cleavage of a protecting group is preferably carried out by hydrolysis in the presence of a base such as, for example, sodium hydroxide solution or potassium hydroxide solution or in the presence of an acid such as, for example, hydrochloric acid or sulphuric acid, in the presence of an aqueous solvent (such as, for example, water/ethanol, water/dioxan or water/tetrahydrofuran) at temperatures of between 50 and 150°C, but preferably at the boiling temperature of the reaction mixture. An imido group, such as the phthalimido group used as a protecting group, is preferably split off with hydrazine in the presence of a solvent such as, for example, water, water/ethanol or water/dioxan at the boiling temperature of the solvent used.

d) For the preparation of compounds of general formula I as hereinbefore defined wherein at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents an alkyl or phenylalkyl group:

Reduction of a compound of general formula VII



(wherein

at least one of the groups  $R_1''$ ,  $R_2''$ ,  $R_3''$   
 5 or  $R_4''$  represents one of the acyl or phenylacyl groups  
 mentioned hereinbefore; and

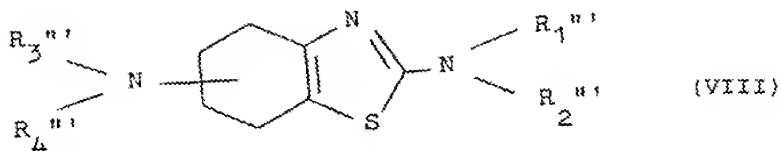
the remaining groups  $R_1''$ ,  $R_2''$ ,  $R_3''$  and  $R_4''$   
 have the meanings given respectively for  $R_1$ ,  $R_2$ ,  
 $R_3$  and  $R_4$  hereinbefore) with a metal hydride.

10 The reduction is conveniently carried out  
 in a suitable solvent (such as, for example, diethylether,  
 tetrahydrofuran, glycoldimethylether or dioxan)  
 with a metal hydride, (e.g. with a complex metal  
 hydride such as, for example, lithium aluminium  
 15 hydride) at temperatures of between 0 and 100°C,  
 but preferably at temperatures of between 20 and  
 80°C.

For the preparation of compounds of general  
 formula I wherein the group  $R_3$  represents one  
 20 of the acyl groups mentioned hereinbefore, it is  
 particularly advantageous to carry out the reaction  
 with lithium aluminium hydride at temperatures  
 of between 0 and 30°C, but preferably at ambient  
 temperature.

25 e) For the preparation of compounds of general  
 formula I as hereinbefore defined wherein at least  
 one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents an  
 alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl  
 groups:

Reaction of a compound of general formula VIII



- (wherein the groups  $R_1'''$ ,  $R_2'''$ ,  $R_3'''$  and  $R_4'''$  are as defined above for  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  respectively with the proviso that at least one of  $R_1'''$ ,  $R_2'''$ ,  $R_3'''$  and  $R_4'''$  represents a hydrogen atom) with a compound of general formula IX



- [wherein  $R_5$  represents an appropriate alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group; and Z represents a nucleophilic leaving group (such as, for example, a halogen atom or a sulphonic acid group, e.g. a chlorine, bromine or iodine atom or a methoxysulphonyloxy or p-toluenesulphonyloxy group); or Z together with an adjacent hydrogen of the group  $R_5$  represents an oxygen atom].

- The reaction is conveniently carried out in the presence of a solvent (such as, for example water, methanol, ethanol, tetrahydrofuran, dioxan, acetone, acetonitrile or dimethylsulphoxide) with an alkylating agent (such as, for example, methyl iodide, dimethyl sulphate, ethyl bromide, diethyl sulphate, allyl iodide, benzyl bromide, 2-phenylethyl bromide or methyl-p-toluene sulphonate), optionally in the presence of a base (such as, for example,

sodium hydroxide solution, potassium carbonate, sodium hydride, potassium-tert.butoxide or triethylamine) conveniently at temperatures of between -10 and 50°C, but preferably at temperatures of between 0 and 30°C. However, the reaction may also be carried out in the absence of a solvent.

Alkylation of the nitrogen atom may also be effected using formaldehyde/formic acid at elevated temperatures (e.g. at the boiling temperature of the reaction mixture) or with a corresponding carbonyl compound and a complex metal hydride (such as, for example, sodium borohydride or sodium cyanoborohydride) in the presence of a solvent (such as, for example, water/methanol, ethanol, ethanol/water, dimethyl formamide or tetrahydrofuran) at temperatures of between 0 and 50°C, but preferably at ambient temperature.

If, according to the invention, a compound of general formula I is obtained wherein at least one of the groups  $R_1$  and  $R_3$  represents a hydrogen atom, this may be converted by corresponding acylation into a corresponding compound of general formula I wherein at least one of the groups  $R_1$  and  $R_3$  represents one of the acyl groups mentioned hereinbefore.

The subsequent acylation is conveniently carried out in the presence of a solvent (such as, for example, methylene chloride, chloroform, carbontetrachloride, ether, tetrahydrofuran, dioxan, glacial acetic acid, benzene, toluene, acetonitrile or dimethylformamide) optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethyl chloroformate, thionylchloride, N,N-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyl-diimidazole or triphenyl-

phosphine/carbontetrachloride, or an agent which activates the amino group (e.g. phosphorus trichloride) and optionally in the presence of an inorganic base (such as, for example, sodium carbonate) or a  
5 tertiary organic base (such as, for example, triethylamine or pyridine, which may itself be used as solvent) at temperatures of between  $-25^{\circ}\text{C}$  and  $250^{\circ}\text{C}$ , but preferably at temperature of between  $-10^{\circ}\text{C}$  and the boiling temperatures of the solvent used. The reaction may  
10 also be carried out in the absence of a solvent and furthermore any water formed during the reaction may be removed by azeotropic distillation (e.g. by heating with toluene using a water separator, or by adding a drying agent such as magnesium sulphate or molecular  
15 sieve).

The compounds of general formula I which have at least one chiral centre can be resolved into their enantiomers by conventional methods e.g. by column chromatography on a chiral phase,  
20 by fractional crystallisation of the diastereomeric salts or by column chromatography of their conjugates with optically active auxiliary acids such as tartaric acid, O,O-dibenzoyl-tartaric acid, camphor acid, camphorsulphonic acid or  $\alpha$ -methoxy-phenylacetic  
25 acid.

The compounds of general formula I obtained from the processes according to the invention may, if desired, subsequently be converted into acid addition salts thereof, particularly the physiologically  
30 acceptable acid addition salts with inorganic or organic acids, for example by conventional methods such as by reacting the compounds as bases with a solution of the corresponding acid in a suitable solvent. Suitable acids include, for example,  
35 hydrochloric, hydrobromic, sulphuric, phosphoric,

lactic, citric, tartaric, succinic, maleic or fumaric acids. Conversely the acid addition salts of the compounds of general formula I obtained may, if desired, subsequently be converted into compounds of general formula I.

The compounds of general formulae II to IX used as starting materials are known from the literature in some cases or may be obtained using methods known from the literature.

Thus, for example, a compound of general formula II may be obtained by halogenation of the corresponding cyclohexanone, which may in turn be prepared by oxidation of the corresponding cyclohexanol and optional subsequent alkylation and/or acylation.

Compounds of general formulae VI, VII and VIII used as starting materials may be obtained by condensation of a corresponding  $\alpha$ -bromo-cyclohexanone with a corresponding thiourea.

The compounds according to the invention wherein at least one of the groups  $R_1$  to  $R_4$  represents one of the acyl groups mentioned hereinbefore may be used as intermediate products for preparing the compounds of general formula I wherein  $R_1$  to  $R_4$  have the meanings given to  $R_1$  to  $R_4$  hereinbefore, with the exception of the acyl groups referred to hereinbefore. These compounds display an effect on blood pressure, a heart rate-lowering effect and an effect on the central nervous system, particularly a stimulant effect on the dopamine receptors.

For example, the following compounds have been tested with regard to their effect on presynaptic dopamine receptors:

A = 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazol-dihydrochloride;

B = 2-amino-6-pyrrolidino-4,5,6,7-tetrahydro-



benzthiazol-dihydrochloride;

C = 2-amino-6-n-propylamino-4,5,6,7-tetrahydro-  
benzthiazol-dihydrochloride;

5 D = 2-allylamino-6-dimethylamino-4,5,6,7-tetrahydro-  
benzthiazol-dihydrochloride;

E = 6-[N-allyl-N-(4-chloro-benzyl)-amino]-2-amino-  
4,5,6,7-tetrahydro-benzthiazol-dihydrochloride;  
and

10 F = 2-amino-6-diallylamino-4,5,6,7-tetrahydro-  
benzthiazol-dihydrochloride.

Initially the effect on the exploratory activity  
of mice was tested and then, after any effect on  
postsynaptic dopamine receptors had been clarified  
(motility in animals pretreated with reserpine),  
15 the effect on dopamine turnover and dopamine synthesis  
was determined.

1. Inhibition of the exploratory activity of  
mice

The exploratory activity of mice in observation  
20 cages each fitted with an infra-red light barrier  
was recorded as the frequency of interruption of  
the light beam by a group of 5 mice within 5 minutes.  
Groups of 5 animals were given the test substance  
by subcutaneous injection, in a dosage of 10 mg/kg,  
25 unless otherwise specified. One hour later the  
animals were moved into the observation cages where  
their exploratory activity over a period of 5 minutes  
was immediately measured. In parallel or alternately  
with groups treated with test substance, control  
30 groups treated with common salt were investigated

(0.9% solution; 0.1 ml/10 g of body weight by subcutaneous route).

The results are displayed in the following table:

5	Substance	Dosage (mg/kg s.c.)	Inhibition of activity compared with controls treated with common salt (in percent)
10	A	2.7 <sup>1</sup>	50
	B	10.0	94
	C	10.0	20 <sup>2</sup>
	D	10.0	76 <sup>2</sup>
15	E	10.0	56 <sup>2</sup>
	F	10.0	60 <sup>2</sup>

- 1) read off from the dosage/activity curve in the range from 1-10 mg/kg subcutaneously
- 2) measurement of exploration: 75 minutes after administration of the substance

## 2. Determination of the inhibition of dopamine turnover

- 25 The inhibition of dopamine turnover was measured in mice. In animals treated with  $\alpha$ -methylparatyrosine (AMPT) (250 mg/kg by intraperitoneal route) 15 minutes into the experiment, the dopamine concentration throughout the brain decreases as the test progresses.
- 30 By the administration of substances which act on autoreceptors, the dopamine reduction (compared with control animals treated with common salt solution) can be inhibited.

Test substances were administered at time

- 17 -

0 of the experiment in a dosage of 5 mg/kg s.c., unless otherwise stated. Four hours and 15 minutes into the experiment the animals were killed and the dopamine in the brains was determined using  
 5 high pressure liquid chromatography with electrochemical detection. This allowed the percentage inhibition of the dopamine reduction induced by AMPT, caused by the test substance, to be calculated.

10	Substance	Dosage (mg/kg s.c.)	% inhibition of AMPT effect
	A	0.95 <sup>1</sup>	50
	B	5	67
15	D	5	52
	E	5	32

1) read off from the dosage/activity curve in the range from 0.5-3 mg/kg s.c.

20 3. Determination of the inhibition of dopamine synthesis

For this purpose, 5 animals were given the test substance in a dosage of 10 mg/kg s.c., unless otherwise stated. After 5 minutes, 750 mg/kg of  
 25  $\gamma$ -butyrolactone were administered, by intraperitoneal route, to rule out the effect of postsynaptic feedback loops on the rate of dopamine synthesis by blocking the presynaptic impulse line. This results in a considerable increase in the synthesis of DOPA  
 30 or dopamine. In order to inhibit the decarboxylation of DOPA, 200 mg/kg of 3-hydroxybenzyl-hydrazine-hydrochloride were administered by intraperitoneal

route after a further 5 minutes. Forty minutes after administration of the test substance the animals were killed and the corpus striatum was prepared. The DOPA content was measured by HPLC with electrochemical detection (standard: dihydroxybenzylamine).

The percentage inhibition of DOPA accumulation stimulated by  $\gamma$ -butyrolactone, produced by the test substance compared with the control animals treated with 0.9% common salt solution was determined.

The results of these experiments are shown in the following table:

15	Substance	Dosage (mg/kg s.c.)	Inhibition of DOPA accumulation compared with controls treated with common salt (in percent)
20	A	0.55 <sup>1</sup>	50
	C	10	60

1) read off from the dosage/activity curve in the range from 0.1-1.0 mg/kg subcutaneously.

4. Determination of the anti-Parkinsonism activity (the activity against Parkinson's disease)

The discovery of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al., Science 219, 979 (1983)) provided an animal model for Parkinson's disease.

The irreversible neurological syndrome triggered by MPTP in man and in monkeys largely resembles

the idiopathic Parkinson's disease in its clinical, pathological, biochemical and pharmacological characteristics (Markey *et al.*, Nature 311, 464 (1984)). The reason for this convincing similarity is that MPTP selectively  
5 destroys the small group of dopaminergic nerve cells in the substantia nigra of the brain which are also destroyed by degenerative processes in naturally occurring Parkinson's disease. It may be that idiopathic Parkinson's disease is caused  
10 by the formation of MPTP or a similar compound in the organism (Snyder, S.H., Nature 311, 514 (1984)). The clinical impression of the MPTP-Parkinson picture has hitherto only been demonstrated in monkeys and man, possibly as a result of its  
15 specific metabolism.

The MPTP model in Rhesus monkeys is therefore exceptionally suitable for testing the activity of anti-Parkinson's disease drugs. Seven Rhesus monkeys were given MPTP (for 3 days, 1 x 0.15 mg/kg  
20 i.m. daily, 3 days break, then 3 days 1 x 0.30-0.40 mg/kg daily) and showed the following symptoms: the animals were akinetic and not capable of taking water or food; they showed a typical bowed posture; occasional cataleptic states occurred; the extremities  
25 showed rigor which was interrupted by clonic convulsions on passive movement; voluntary movements of the rump and the extremities could not usually be triggered even by very powerful and painful stimulation.

After intramuscular administration of compound  
30 C (10-100 ug/kg) voluntary movements first occurred after a time interval of 5 to 10 minutes, which were followed in the subsequent 10 to 30 minutes by a gradual but extensive normalisation of the motor function. The animals were capable of taking  
35 food. They stayed perfectly upright and straight inside their cages and were also satisfactory in terms of their vigilance and species-specific behaviour.

The only residual symptoms recorded were an occasional transient and slight resting tremor and a reduction in rough strength. There was no sedation. Circulation in the skin appeared to be greater than before  
5 the compound C was administered.

The effect of compound C diminished after about 5 to 7 hours and the animals reverted to the Parkinson symptoms described above; a fresh administration of this compound again led to an  
10 improvement or substantial removal of the clinically pathological manifestations. The advantageous effects of the compounds were thus reproduced several times in each individual animal.

No side effects were detected at the dosages  
15 used hitherto.

Moreover, the compounds prepared according to the invention are largely non-toxic. Thus, when the substances were tested in mice at dosages of between 27 and 50 mg/kg s.c., no deaths were  
20 recorded.

In view of their pharmacological properties, the compounds of general formula I prepared according to the invention and the physiologically acceptable acid addition salts thereof are suitable for the  
25 treatment of central nervous, neuropsychiatric diseases, particularly schizophrenia, for the treatment of Parkinsonism or Parkinson's disease and/or for treating circulatory disorders, particularly hypertension.

According to a yet further feature of the  
30 present invention there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of general formula I as hereinbefore defined or a physiologically acceptable acid addition salt thereof in association with one or more pharmaceutical  
35 carriers and/or excipients.

For pharmaceutical administration the active ingredient may be incorporated into preparations

in either liquid or solid form using carriers and excipients conventionally used in the pharmaceutical art, optionally in combination with other active ingredients. Preferred forms include, for example, 5 plain or coated tablets, powders, suppositories, suspensions, drops or ampoules.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage 10 units contain from 0.01 to 0.5 mg/kg of body weight, preferably from 0.1 to 0.3 mg/kg of body weight, and the daily dose may, for example, consist of 1 to 4 dosage units. The total daily dose may, however, be varied according to the compound used, 15 the subject treated and the complaint concerned.

According to a still further feature of the present invention there is provided a method of treating a patient suffering from, or susceptible to, central nervous, neuropsychiatric diseases, 20 particularly schizophrenia, Parkinsonism or Parkinson's disease and/or circulatory disorders, particularly hypertension, which comprises administering to the said patient an effective amount of a compound of general formula I as hereinbefore defined or 25 a physiologically acceptable acid addition salt thereof.

The following non-limiting examples are intended to illustrate the invention in more detail:

Example A4-[N-(4-Chloro-benzyl)-amino]-cyclohexanol

- 75.8 g (0.5 Mol) of 4-amino-cyclohexanol-hydrochloride are dissolved in 60 ml of water and, after the addition of 36 g (0.26 Mol) of potassium carbonate and 500 ml of toluene, boiled with a water separator until the separation of water is complete. Then 71.7 g (0.5 Mol) of 4-chlorobenzaldehyde are slowly added with further boiling using the water separator. After the calculated quantity of water has been separated, the residue is added to water and the toluene phase is separated off and concentrated. The concentration residue is dissolved in 500 ml of ethanol and 19 g (0.5 Mol) of sodium borohydride are added in batches with stirring. After standing overnight, the mixture is concentrated, mixed with water and extracted with chloroform. After drying and concentrating the extracts, the residue is recrystallised from ethyl acetate.

Yield: 93.4 g (78% of theory),

M.p.: 103-104°C

Calculated: C 65.12 H 7.57 N 5.84 Cl 14.79

Found: 65.21 7.68 5.93 14.65

- The following compound was prepared analogously to Example A using propionaldehyde:

4-n-propylamino-cyclohexanol

Yield: 12.4% of theory,

M.p.: < 20°C

- Calculated: m/e = 157

Found: m/e = 157

Example B4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanol

- 7.2 g (30 mMol) of 4-[N-(4-chloro-benzyl)-amino]-cyclohexanol are dissolved in 30 ml of dimethylformamide, and after the addition of 2.2 g (16 mMol)



- of potassium carbonate, 4.26 g (30 mMol) of methyl iodide are added dropwise. When the slightly exothermic reaction is complete, the mixture is concentrated by evaporation, mixed with water and extracted with
- 5 chloroform. The concentrated extracts are chromatographed on silica gel to purify them (eluant: methylene chloride/methanol = 20/1).
- Yield: 3.3 g (43.4% of theory),  
M.p.: 74-75°C
- 10 Calculated: C 66.26 H 7.94 N 5.52 Cl 13.97  
Found: 66.36 7.95 5.46 13.81

The following compounds were prepared analogously to Example B:

15

4-Hexamethyleneimino-cyclohexanol

Prepared from 4-amino-cyclohexanol and 1,6-dibromohexane.

Yield: 47.3% of theory,

20 M.p.: < 20°C

Calculated: m/e = 197

Found: m/e = 197.

4-Diallylamino-cyclohexanol

25

Prepared from 4-amino-cyclohexanol and allylbromide.

Yield: 51% of theory,

M.p.: < 20°C

Calculated: m/e = 195

30 Found: m/e = 195.

4-Piperidino-cyclohexanol

Prepared from 4-amino-cyclohexanol and 1,5-dibromopentane.

35 Yield: 65.8% of theory,

M.p.: < 20°C

Calculated:  $m/e = 183$   
Found:  $m/e = 183$ .

4-Pyrrolidino-cyclohexanol

5

Prepared from 4-amino-cyclohexanol and 1,4-dibromo-butane.

Yield: 35.8% of theory,

M.p.:  $< 20^{\circ}\text{C}$

10 Calculated:  $m/e = 169$   
Found:  $m/e = 169$ .

Example C

4-Diethylamino-cyclohexanol

15

28.75 g (0.25 Mol) of 4-amino-cyclohexanol are dissolved in 150 ml of water, with the addition of 20 g (0.5 Mol) of sodium hydroxide and then 65.6 ml (0.5 Mol) of diethylsulphate are added dropwise.

20 The mixture then heats up to  $65^{\circ}\text{C}$ . It is stirred at  $70^{\circ}\text{C}$  for one hour and then poured onto ice and extracted with chloroform.

Yield: 18.2 g (42.5% of theory),

M.p.:  $< 20^{\circ}\text{C}$

25 Calculated:  $m/e = 171$   
Found:  $m/e = 171$ .

Example D

4-[N-(4-Chloro-benzyl)-amino]-cyclohexanone

30

23.9 g (0.1 Mol) of 4-[N-(4-chlorobenzyl)-amino]-cyclohexanol are suspended in 125 ml of ice water and then 32 ml of concentrated sulphuric acid are added. Then 29.4 g (0.1 Mol) of potassium  
35 dichromate are added in 2 batches and the mixture is heated for 5 hours at  $50^{\circ}\text{C}$ . It is then cooled, made alkaline with sodium hydroxide solution and

then extracted with chloroform. After concentration, a yellowish oily liquid is obtained.

Yield: 8.2 g (34% of theory),

M.p.: < 20°C

5 Calculated: m/e = 237/239

Found: m/e = 237/239.

The following compounds were prepared analogously to Example D:

10

4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanone

Yield: 38% of theory,

M.p.: < 20°C

15 Calculated: m/e = 251/253

Found: m/e = 251/253.

4-Diallylamino-cyclohexanone

20 Yield: 21% of theory,

M.p.: < 20°C

Calculated: m/e = 193

Found: m/e = 193.

25 4-Piperidino-cyclohexanone

Yield: 22.2% of theory,

M.p.: < 20°C

Calculated: m/e = 181

30 Found: m/e = 181.

4-Pyrrolidino-cyclohexanone

Yield: 45.1% of theory,

35 M.p.: < 20°C

Calculated: m/e = 167

Found: m/e = 167.

## 4-Diethylamino-cyclohexanone

Yield: 49.7% of theory,

M.p.: &lt; 20°C

Calculated: m/e = 169

5 Found: m/e = 169.

## 4-n-Propylamino-cyclohexanone

Yield: 33% of theory,

M.p.: &lt; 20°C

Calculated: m/e = 155

10 Found: m/e = 155.

Example E4-[N-(4-Chloro-benzyl)-methylamino]-cyclohexanone

8.4 g (35 mMol) of 4-[N-(4-chloro-benzyl)-  
15 amino]-cyclohexanone are dissolved in 50 ml of  
absolute dimethylformamide and, after the addition  
of 2.6 g (18.7 mMol) of potassium carbonate, 5.0 g  
(35 mMol) of methyl iodide are added dropwise at  
25-30°C. After standing overnight the mixture  
20 is concentrated, mixed with water and extracted  
with chloroform. The extracts are dried and concentrated.  
Yield: 8.1 g (93% of theory),  
M.p.: < 20°C  
Calculated: m/e = 251/253  
25 Found: m/e = 251/253.

The following compounds were prepared analogously  
to Example E:

## 4-[N-Allyl-N-(4-chloro-benzyl)-amino]-cyclohexanone

Yield: 70.7% of theory,

30 M.p.: &lt; 20°C

Calculated:  $m/e = 277/279$   
Found:  $m/e = 277/279$ .

4-[N-(4-Chloro-benzyl)-ethylamino]-cyclohexanone

5

Yield: 30% of theory,  
M.p.:  $< 20^{\circ}\text{C}$   
Calculated:  $m/e = 265/267$   
Found:  $m/e = 265/267$ .

10

Example F  
4-Hexamethyleneimino-cyclohexanone

A solution of 47 g (0.5 Mol) of 4-hexamethyleneimino-  
15 cyclohexanol in 300 ml of methylenechloride is added  
dropwise to a suspension of 107.5 g (0.5 Mol) of pyridinium  
chlorochromate and 40 g (0.5 Mol) of sodium acetate in  
700 ml of methylenechloride at 20 to 25°C. After stirring  
for one hour at 20°C, the mixture is poured onto ice water  
20 and sodium hydroxide solution, and then extracted with  
methylene chloride. After drying and concentration of the  
extracts a coloured oily liquid is left.  
Yield: 16.8 g (35.8% of theory),  
M.p.:  $< 20^{\circ}\text{C}$   
25 Calculated:  $m/e = 195$   
Found:  $m/e = 195$ .

Example 12-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

2.82 g (0.02 Mol) of 4-dimethylamino-cyclohexanone  
5 are dissolved in 20 ml of glacial acetic acid,  
mixed with 4.7 ml of 36% of hydrobromic acid in  
glacial acetic acid and then a solution of 1.0 ml  
(0.02 Mol) of bromine in 12 ml of glacial acetic  
acid is added dropwise with cooling. The mixture  
10 is then concentrated by evaporation in vacuo and  
the residue is triturated several times with diethylether.  
The ether extracts are discarded and the residue  
is dissolved in 50 ml of ethanol. After 3.04 g  
(40 mmol) of thiourea have been added the mixture  
15 is refluxed for 5 hours. It is then concentrated  
by evaporation, made alkaline with sodium hydroxide  
solution and extracted with chloroform. After  
drying and concentration of the extracts, the residue  
is purified by column chromatography on silica  
20 gel (eluant: chloroform/methanol = 1/1). Then  
the base (mp: 191°C) is dissolved in acetone and  
converted into the dihydrochloride with isopropanolic  
hydrochloric acid.

Yield: 1.09 g (20% of theory),

25 M.p.: 272°C

Calculated:	C 40.00	H 6.34	N 15.55	Cl 26.24
Found:	39.63	6.55	15.31	26.29

The following tetrahydrobenzthiazoles were  
prepared analogously to Example 1 from the corresponding  
30 ketones:

2-Amino-6-diethylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 25% of theory,

M.p.: 182-183°C

Calculated: C 58.62 H 8.49 N 18.64

Found: 58.65 8.72 18.50

2-Amino-6-piperidino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 13% of theory,

5 M.p.: 280°C

Calculated: C 46.45 H 6.82 N 13.55 Cl 22.85

Found: 46.37 6.75 13.41 22.95

2-Amino-6-pyrrolidino-4,5,6,7-tetrahydro-benzthiazole

Yield: 24.4% of theory,

10 M.p.: 204-206°C

Calculated: C 59.15 H 7.67 N 18.81

Found: 59.50 7.74 18.95

2-Amino-6-diallylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

15 Yield: 19% of theory,

M.p.: 242°C

Calculated: C 48.44 H 6.56 N 13.03 Cl 22.00

Found: 47.90 6.49 12.95 22.21

2-Amino-6-[N-(4-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole

20 Yield: 35% of theory,

M.p.: 146°C

Calculated: C 57.23 H 5.49 N 14.30 Cl 12.06

Found: 56.93 5.56 13.86 12.04

2-Amino-6-[N-(4-chloro-benzyl)-methylamino]-4,5,6,7-tetrahydro-benzthiazole

Yield: 36% of theory,

M.p.: 163°C

Calculated: C 58.69 H 5.89 N 13.64 Cl 11.51

30 Found: 58.50 5.94 13.49 11.55

2-Amino-6-[N-(4-chloro-benzyl)-ethylamino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 49% of theory,

M.p.: 258°C (decomposition)

5	Calculated:	C 48.67	H 5.61	N 10.64	Cl 26.94
	Found:	48.30	5.85	10.57	26.97

2-Amino-6-[N-allyl-N-(4-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 46.5% of theory,

10 M.p.: 240°C (decomposition)

	Calculated:	C 50.19	H 5.45	N 10.33	Cl 26.14
	Found:	49.84	5.68	9.97	26.04

2-Amino-6-hexamethyleneimino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

15 Yield: 15.4% of theory,

M.p.: 295°C (decomposition)

	Calculated:	C 48.17	H 7.14	N 12.95	Cl 21.86
	Found:	47.90	7.34	12.44	21.64

20 2-Allylamino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 4-dimethylamino-cyclohexanone  
by bromination and subsequent reaction with allylthiourea.  
Yield: 64% of theory,

M.p.: 248°C

25	Calculated:	C 46.45	H 6.82	N 13.54	Cl 22.85
	Found:	46.30	7.00	13.29	22.99

2-Amino-5-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 3-dimethylamino-cyclohexanone.

30 Yield: 33% of theory,

M.p.: 194°C

	Calculated:	C 40.00	H 6.34	N 15.55	Cl 26.24
	Found:	39.74	6.37	15.15	25.96



2-Amino-5-morpholino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 3-morpholino-cyclohexanone.

Yield: 7.4 g (20% of theory),

5 M.p.: 237-238°C

Calculated: C 42.31 H 6.13 N 13.46

Found: 42.00 6.29 13.13

Example 2

10 2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

a) 4-(Phthalimido)-cyclohexanol

75.5 g (0.5 Mol) of 4-aminocyclohexanol-hydrochloride and 74.0 g (0.5 Mol) of phthalic acid anhydride

- are mixed with 65 g (0.5 Mol) of ethyl-diisopropyl-  
15 amine and 1000 ml of toluene and boiled for 36 hours with a water separator. Water is then added, the toluene phase is separated off and the aqueous phase is extracted several times with chloroform. The organic phases are combined, dried and concentrated.  
20 The concentration residue is recrystallised from isopropanol.  
Yield: 95 g (77.8% of theory),  
M.p.: 175-176°C.

b) 4-(Phthalimido)-cyclohexanone

- 25 95 g (0.388 Mol) of 4-(phthalimido)-cyclohexanol are dissolved in 600 ml of chloroform and, after the addition of 450 ml of water and 120 ml of sulphuric acid, 90 g (0.3 Mol) of potassium dichromate are added in batches. The internal temperature of  
30 the mixture is maintained at between 25 and 30°C by slight cooling. The mixture is stirred for a further 3 hours and then the chloroform phase is separated off and the mixture extracted twice more with chloroform. After drying and concentration of the extracts

82 g (86.9% of theory) are obtained.

c) 2-Amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole

48.6 g (0.2 Mol) of 4-(phthalimido)-cyclohexanone  
5 are brominated analogously to Example 1 with 32 g  
(0.2 Mol) of bromine and then converted with thiourea  
into the 2-amino-6-phthalimido-4,5,6,7-tetrahydro-  
benzthiazole.

Yield: 30 g (50% of theory),

10 M.p.: 244-246°C (decomposition)

Calculated: C 60.18 H 4.38 N 14.04

Found: 60.05 4.25 13.95

d) 2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

15 9.5 g (31.7 mMol) of 2-amino-6-phthalimido-  
4,5,6,7-tetrahydro-benzthiazole are suspended in  
100 ml of ethanol and, after the addition of 1.8 g  
(36 mMol) of hydrazine hydrate, refluxed for 2  
hours. The mixture is then concentrated and purified  
20 by column chromatography on silica gel using methanol  
as eluant. The dihydrochloride is precipitated  
with ethanolic hydrochloric acid.

Yield: 2.0 g (26% of theory),

M.p.: > 315°C (decomposition)

25 Calculated: C 34.72 H 5.41 N 17.35 Cl 29.25

Found: 35.00 5.26 16.95 29.10

Example 3

30 6-Acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide

160 g (1.0 Mol) of bromine are added dropwise  
to a solution of 155 g (1.0 Mol) of 4-acetylamino-

cyclohexanone in 1.5 l of glacial acetic acid.  
The mixture is stirred for 3 hours at ambient temperature.  
152.0 g (2.0 Mol) of thiourea are added to the  
reaction mixture and the resulting mixture is refluxed  
5 for 30 minutes. After cooling, the precipitated crystals  
are suction filtered and washed with water and acetone.  
Yield: 73 g (37% of theory),  
M.p.: 292-293°C (decomposition)

10 Calculated: C 36.99 H 4.83 N 14.38  
Found: 36.82 4.76 14.18

By stirring the hydrobromide in aqueous potassium  
carbonate solution and subsequently suction filtering,  
the free base is obtained, m.p. 194-196°C (methanol).

15 The following compounds were prepared analogously  
to Example 3:

6-Acetylamino-2-allylamino-4,5,6,7-tetrahydro-benzthiazole  
Yield: 46% of theory,  
M.p.: 194-196°C

Calculated: m/e = 251  
20 Found: m/e = 251

6-Acetylamino-2-methylamino-4,5,6,7-tetrahydro-  
benzthiazole  
Yield: 64% of theory,  
M.p.: 238-240°C

25 Calculated: C 53.30 H 6.71 N 18.65  
Found: 53.18 6.78 18.41

6-Acetylamino-2-dimethylamino-4,5,6,7-tetrahydro-  
benzthiazole  
Yield: 51% of theory,

30 M.p.: 170-171°C  
Calculated: C 55.20 H 7.16 N 17.56  
Found: 55.15 7.17 17.58

Example 4

2,6-Diamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide

- 3 g (0.01 Mol) of 6-acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide are dissolved  
5 in 20 ml of semi-concentrated hydrobromic acid and refluxed for 6 hours. The solution is then concentrated by evaporation and the residue recrystallised from methanol.  
Yield: 2.8 g (82% of theory),  
10 M.p.: >315°C,  
Melting point of the base: 233-236°C  
Calculated: C 25.39 H 3.96 N 12.69  
Found: 25.34 3.93 12.51

- The following compounds were prepared analogously  
15 to Example 4:

- 6-Amino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole-hydrobromide  
Yield: 57% of theory,  
M.p.: 262-263°C  
20 Calculated: C 36.37 H 5.34 N 15.90  
Found: 36.30 5.45 15.82  
  
2-Allylamino-6-amino-4,5,6,7-tetrahydro-benzthiazole-oxalate  
Yield: 52% of theory,  
25 M.p.: 164-165°C (decomp.)  
Calculated: m/e = 209  
Found: m/e = 209  
  
6-Amino-2-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide  
30 Yield: 45% of theory,  
M.p.: >270°C (decomp.)  
Calculated: C 30.10 H 4.77 N 11.70

- 35 -

Found: 30.13 4.84 11.68

Example 5

5 2-Amino-6-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-  
benzthiazole-dihydrochloride

5 g (0.022 Mol) of 2-phenyl-ethylbromide and 2.6 g of potassium carbonate are added to a solution of 3.4 g (0.02 Mol) of 2,6-diamino-tetrahydro-benzthiazole in 34 ml of dimethylformamide and the reaction  
10 mixture is stirred at 100°C for 3 hours. The potassium bromide precipitate is then suctioned off and the solvent is distilled off. The residue is chromatographed on silica gel (ethyl acetate/methanol = 80/20 + 3% ammonia). The desired compound crystallises  
15 out from ethereal hydrochloric acid.

Yield: 2.1 g (30% of theory),

M.p.: 289-291°C

Calculated: C 52.02 H 6.11 N 12.13

Found: 51.82 6.13 12.16

20 The following compounds were prepared analogously to Example 5:

2-Amino-6-isopropylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 28% of theory,

25 M.p.: 295-296°C (decomp.)

Calculated: C 42.25 H 6.74 N 14.78

Found: 41.95 7.09 14.50

2-Amino-6-isobutylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

30 Yield: 35% of theory,

M.p.: 268°C (decomp.)

Calculated: C 44.29 H 7.10 N 14.09

Found: 43.97 7.17 13.97

6-Allylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 38% of theory,

M.p.: 282-283°C (decomp.)

5 Calculated: C 42.56 H 6.07 N 14.89  
Found: 42.17 6.07 14.71

2-Amino-6-[N-(2-chloro-benzyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 40% of theory,

10 M.p.: > 280°C (decomp.)

Calculated: C 45.85 H 4.95 N 11.45  
Found: 45.50 4.86 11.08

2-Amino-6-propargylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

15 Yield: 35% of theory,

M.p.: 268-270°C (decomp.)

Calculated: C 42.86 H 5.40 N 15.00  
Found: 42.78 5.59 14.79

2-Amino-6-methylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrobromide

20

Yield: 25% of theory,

M.p.: 312-313°C (decomp.)

Calculated: C 27.84 H 4.38 N 12.18  
Found: 27.78 4.46 12.21

25

#### Example 6

2-Amino-6-di-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride-monohydrate

30 To a solution of 3.4 g (0.02 Mol) of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole in 50 ml of methanol are added 10 g (0.08 Mol) of n-propylbromide and 11.1 g of potassium carbonate and the mixture is refluxed for 3 days. 100 ml of water are

added and the mixture is extracted with ethylacetate. The solvent is distilled off and the residue is chromatographed on silica gel (eluant: methylenechloride/methanol = 80/20). The corresponding fraction  
 5 is concentrated by evaporation and the desired compound is precipitated in the form of the hydrochloride. Yield: 1.9 g (28% of theory),  
 M.p.: 271-273°C

Calculated: C 45.34 H 7.90 N 12.20  
 10 Found: 45.00 7.98 12.00

#### Example 7

#### 2-Amino-6-n-butylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

15 To a solution of 3.4 g (0.02 Mol) of 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole in 34 ml of dimethylformamide are added 1.8 g (0.022 Mol) of n-butanal and the mixture is heated to 50°C for 1 hour. After cooling, the reaction solution  
 20 is mixed with 0.8 g (0.02 Mol) of sodium borohydride and heated to 50°C for 30 minutes. The solvent is largely eliminated in vacuo. Whilst cooling with ice, the residue is mixed with 20 ml of water and 2N hydrochloric acid until a pH of 1 is obtained.  
 25 The aqueous solution is extracted with ethylacetate and the organic phase discarded. The aqueous phase is mixed with potassium carbonate until an alkaline reaction is obtained and then extracted with ethyl acetate. The organic phase is dried and concentrated.  
 30 The compound crystallizes out when ethereal hydrochloric acid is added.

Yield: 2.3 g (39% of theory),

M.p.: 254-256°C

Calculated: C 44.29 H 7.10 N 14.09  
 35 Found: 44.44 7.31 14.07

The following compounds were prepared analogously to Example 7:

- 2-Amino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- 5 Yield: 38% of theory,  
M.p.: 296-297°C  
Calculated: C 40.00 H 6.34 N 15.55  
Found: 39.97 6.41 15.35
- 2-Amino-6-n-pentylamino-4,5,6,7-tetrahydro-benzthiazole-semifumarate
- 10 Yield: 42% of theory,  
M.p.: >270°C  
Calculated: C 56.54 H 7.79 N 14.13  
Found: 56.13 7.80 13.97
- 2-Amino-6-n-hexylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- 15 Yield: 49% of theory,  
M.p.: 272-274°C  
Calculated: C 47.85 H 7.72 N 12.88  
20 Found: 47.96 7.65 12.71
- 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- 25 Yield: 42% of theory,  
M.p.: 286-288°C  
Calculated: C 42.25 H 6.74 N 14.78  
Found: 42.05 6.77 14.57
- (-)-2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- M.p.: 270-272°C  
 $\alpha_D^{20} = -56^\circ$  (c = 1, methanol)



(+) 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole dihydrochloride

M.p.: 270-272°C

$\alpha_D^{20} = +56^\circ$  (c = 1, methanol)

5 2-Amino-6-cyclopentylamino-4,5,6,7-tetrahydro-benzthiazole-dioxalate

Yield: 36% of theory,

M.p.: 212-213°C

Calculated: C 46.04 H 5.55 N 10.07

10 Found: 45.95 5.28 10.08

2-Amino-6-cyclohexylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 38% of theory,

M.p.: 288-290°C

15 Calculated: C 48.14 H 7.15 N 12.96

Found: 47.88 7.16 12.74

#### Example 8

20 6-Ethylamino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

A solution of 1 g (4.4 mMol) of 6-acetylamino-2-methylamino-4,5,6,7-tetrahydro-benzthiazole in 20 ml of absolute tetrahydrofuran is mixed with 0.4 g (0.01 Mol) of lithium aluminium hydride and  
25 refluxed for 2 hours. After cooling, 50 g of a 40% diammonium tartrate solution are added dropwise. The organic phase is separated off and concentrated by evaporation. The residue is chromatographed on silica gel (eluant: methylene chloride/methanol =  
30 80/20). The corresponding fraction is concentrated by evaporation. The compound crystallizes out when ethereal hydrochloric acid is added.

Yield: 0.3 g (33% of theory),

M.p.: > 260°C

35 Calculated: m/e = 211

Found: m/e = 211

The following compounds were prepared analogously to Example 8:

- 2-Allylamino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-  
 5 dihydrochloride  
 Yield: 37% of theory,  
 M.p.: 218-220°C (decomp.)  
 Calculated: C 46.45 H 6.82 N 13.54  
 Found: 46.60 7.03 13.66
- 10 2-Dimethylamino-6-ethylamino-4,5,6,7-tetrahydro-  
 benzthiazole-oxalate hydrate  
 Yield: 20% of theory,  
 M.p.: 189-190°C  
 Calculated: C 46.83 H 6.95 N 12.60  
 15 Found: 47.03 6.89 12.49

Example 9

6-Acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-  
 benzthiazole

- 20 To a solution of 4.2 g (0.02 Mol) of 6-acetylamino-  
 2-amino-4,5,6,7-tetrahydro-benzthiazole in 100 ml  
 of absolute tetrahydrofuran are added 2.2 g (0.022 Mol)  
 of triethylamine and 3.1 g (0.022 Mol) of benzoylchloride  
 and the mixture is refluxed for 3 hours. The reaction  
 25 mixture is mixed with water and extracted with  
 ethyl acetate. The organic phase is concentrated  
 by evaporation. The residue is recrystallized  
 from methanol.  
 Yield: 3 g (48% of theory),  
 30 M.p.: > 260°C  
 Calculated: m/e = 315  
 Found: m/e = 315

The following compounds were prepared analogously to Example 9:

2,6-Diacetylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 50% of theory,

5 M.p.: 258-259°C

Calculated: m/e = 252

Found: m/e = 252

6-Acetylamino-2-propionylamino-4,5,6,7-tetrahydro-benzthiazole

10 Yield: 44% of theory,

M.p.: > 260°C

Calculated: m/e = 266

Found: m/e = 266

6-Acetylamino-2-phenylacetylamino-4,5,6,7-tetrahydro-benzthiazole

15 Yield: 78% of theory,

M.p.: 112°C

Calculated: m/e = 329

Found: m/e = 329

20

#### Example 10

2-Benzylamino-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-  
dihydrochloride

To a solution of 1.2 g (3.2 mmol) of 6-acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-benzthiazole in 50 ml of absolute tetrahydrofuran are added 0.24 g (64 mmol) of lithium aluminium hydride and the mixture is refluxed for 1 hour. It is then worked up as in Example 8.

30 Yield: 0.4 g (34% of theory),

M.p.: 242-245°C

Calculated: C 53.33 H 6.43 N 19.68

Found: 53.59 6.37 19.42

The following compounds were prepared analogously to Example 10:

- 2,6-Diethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- 5 Yield: 38% of theory,  
M.p.: 241-243°C  
Calculated: C 44.29 H 7.10 N 14.09  
Found: 44.06 7.27 13.85
- 6-Ethylamino-2-n-propylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- 10 Yield: 32% of theory,  
M.p.: 267-268°C  
Calculated: C 46.15 H 7.42 N 13.46  
Found: 45.95 7.53 13.33
- 6-Ethylamino-2-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride-hemihydrate
- 15 Yield: 26% of theory,  
M.p.: 248-251°C  
Calculated: C 53.25 H 6.84 N 10.96  
20 Found: 53.31 6.64 10.89
- 2-(4-Chloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- Yield: 65% of theory,  
M.p.: >260°C
- 25 Calculated: C 48.67 H 5.62 N 10.64  
Found: 48.79 5.80 10.60
- 2-(2-Chloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride
- Yield: 36% of theory,  
M.p.: 251-253°C
- 30 Calculated: C 48.67 H 5.62 N 10.64  
Found: 48.57 5.78 10.57

2-(3,4-Dichloro-benzylamino)-6-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Yield: 62.5% of theory,

M.p.: > 260°C

5 Calculated: C 44.77 H 4.93 N 9.79  
Found: 44.85 4.82 9.96

6-Acetylamino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 2,6-diacetylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

Yield: 33% of theory,

M.p.: 234-235°C

Calculated: m/e = 238

Found: m/e = 238

15

6-Acetylamino-2-benzylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 6-acetylamino-2-benzoylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

20

6-Acetylamino-2-n-propylamino-4,5,6,7-tetrahydro-benzthiazole

Prepared from 6-acetylamino-2-propionylamino-4,5,6,7-tetrahydro-benzthiazole at ambient temperature.

25

6-Acetylamino-2-[N-(2-phenyl-ethyl)-amino]-4,5,6,7-tetrahydro-benzthiazole.

Example 11

30 6-Amino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Prepared from 6-acetylamino-2-ethylamino-4,5,6,7-tetrahydro-benzthiazole analogously to

35 Example 4.

Yield: 45% of theory,

M.p.: 155-158°C

Calculated:	C 40.00	H 6.34	N 15.55
Found:	39.86	6.31	15.26

The following compounds were prepared analogously  
5 to Example 11:

6-Amino-2-benzylamino-4,5,6,7-tetrahydro-  
benzthiazole-dihydrobromide

6-Amino-2-n-propylamino-4,5,6,7-tetrahydro-  
10 benzthiazole-dihydrobromide

6-Amino-2-[N-(2-phenyl-ethyl)amino]-4,5,6,7-  
tetrahydro-benzthiazole-dihydrobromide.

#### Example 12

15 2-Benzoylamino-6-dimethylamino-4,5,6,7-tetrahydro-  
benzthiazole-dihydrochloride

3.0 g (15 mMol) of 2-amino-6-dimethylamino-  
4,5,6,7-tetrahydro-benzthiazole are dissolved in  
20 15 ml of pyridine and 2.1 g (15 mMol) of benzoylchloride  
are added dropwise. After standing overnight the  
mixture is concentrated, mixed with soda solution  
and extracted with chloroform. The chloroform  
extract is concentrated and then chromatographed  
25 on silica gel (eluant: methylenechloride/methanol =  
9/1). The isolated base (melting point 174°C)  
is dissolved in acetone and the dihydrochloride  
is precipitated with isopropanolic hydrochloric  
acid.

30 Yield: 2.8 g (49% of theory),

M.p.: 284°C (decomp.)

Calculated:	C 51.33	H 5.65	N 11.23	Cl 18.94
Found:	51.51	5.76	11.32	18.75

Example 136-Acetylamino-2-amino-4,5,6,7-tetrahydro-benzthiazole

3.1 g (20 mMol) of 4-acetylamino-cyclohexanone  
and 6.2 g (20 mMol) of formamidine-disulphide-dihydrobromide  
5 are intimately mixed and heated at a temperature  
of 120 - 130°C for 2 hours with stirring. The  
mixture is then taken up in water, made alkaline  
with ammonia and extracted with chloroform. After  
the extracts have been dried they are concentrated  
10 by evaporation, triturated with acetone and suction  
filtered.

Yield: 1.8 g (42.6% of theory),

M.p.: 195°C

Calculated: C 51.17 H 6.20 N 19.89

15 Found: 51.09 6.22 19.75

Starting from 4-dimethylamino-cyclohexanone  
the following compound was prepared analogously  
to Example 13:

20

2-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole

Yield: 21% of theory,

M.p.: 189-190°C

Calculated: C 54.80 H 7.66 N 21.29

25 Found: 54.71 7.53 21.12

Example I

Tablet core containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

## Composition:

5	1 tablet core contains:	
	Active substance	5.0 mg
	Lactose	33.5 mg
	Corn starch	10.0 mg
	Gelatine	1.0 mg
10	Magnesium stearate	<u>0.5 mg</u>
		50.0 mg

Preparation

- 15 A mixture of the active substance with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a screen with a mesh size of 1 mm, dried at 40°C and again rubbed through this screen. The granulate thus obtained is mixed with magnesium stearate and compressed to form
- 20 tablet cores. The tablets must be prepared in darkened rooms.

Weight of core: 50 mg  
Punch: 4 mm, convex.

- 25 The tablet cores thus obtained are coated by the usual method with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with bees wax.

Weight of coated tablet: 100 mg.



Example II

Drops containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

Composition:

5	100 ml of drops substance:	
	Methylester-p-hydroxybenzoate	0.035 g
	n-Propylester-p-hydroxybenzoate	0.015 g
	Anisol	0.05 g
	Menthol	0.06 g
10	Pure ethanol	10.0 g
	Active substance	0.5 g
	Citric acid	0.7 g
	Sec. sodiumphosphate x 2 H <sub>2</sub> O	0.3 g
	Sodium cyclamate	1.0 g
15	Glycerol	15.0 g
	Distilled water	ad 100.0 ml

Preparation

20 The p-hydroxybenzoates, anisol and menthol are dissolved in ethanol (Solution I).

The buffer substances, active substance and sodium cyclamate are dissolved in distilled water and glycerol is added (Solution II). Solution I is stirred into Solution II and the mixture is  
25 topped up to the volume specified with distilled water. The finished drops solution is filtered through a suitable filter. The preparation and bottling of the drops solution must be carried out away from the light and under a protective  
30 gas.

Example III

Suppositories containing 10 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

- 5 1 suppository contains:

Active substance 10.0 mg

Suppository mass  
(e.g. Witepsol\*W 45) 1 690.0 mg

1 700.0 mg

- 10 Preparation

The finely powdered substance is stirred into the molten suppository mass, cooled to 40°C, with an immersion homogeniser. At 35°C the mass is poured into slightly chilled moulds.

- 15 Weight of suppository: 1.7 g

Example IV

Ampoules containing 5 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

- 20 1. Ampoule contains:

Active substance 5.0 mg

Citric acid 7.0 mg

Sec. sodium phosphate x 2H<sub>2</sub>O 3.0 mg

Sodium pyrosulphite 1.0 mg

- 25 Distilled water ad. 1.0 ml

Preparation

- 30 The buffer substances, active substance and sodium pyrosulphite are successively dissolved in deionised water which has been cooled under CO<sub>2</sub> gas. The solution is made up to the volume specified with boiled water and filtered free from pyrogens.

\* Trade Mark

Bottling: in brown ampoules under protective gas  
 Sterilisation: 20 minutes at 120°C.

The preparation and transferring of the ampoule solution must be carried out in darkened rooms.

5

Example V

Coated tablets containing 1 mg of 2-amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride

1 tablet core contains:

10	Active substance	1.0 mg
	Lactose	35.5 mg
	Corn starch	12.0 mg
	Gelatine	1.0 mg
	Magnesium stearate	<u>0.5 mg</u>
15		50.0 mg

Preparation

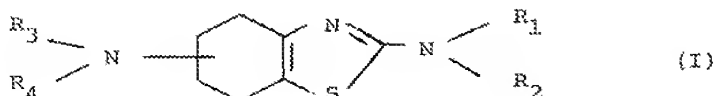
Analogous to Example I

	Weight of core:	50 mg
20	Punch: :	5 mm, convex
	Weight of coated tablet:	100 mg

Obviously, instead of the compound mentioned, all the other compounds of general formula I may be incorporated as active substance in the Pharmaceutical  
 25 Examples I to V, such as, for example, 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydro-benzthiazole-dihydrochloride.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for preparing a compound of general formula I



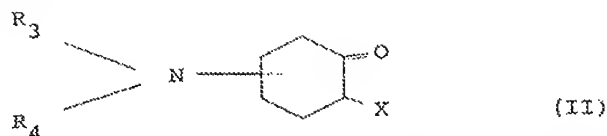
[wherein

$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms in the alkyl part or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

$R_2$  represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

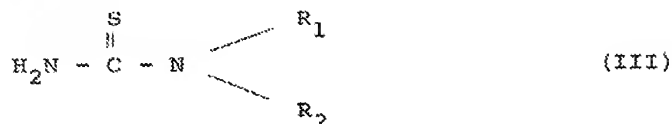
$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms in the alkyl part or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms), and  $R_4$  represents a hydrogen

atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group] or an acid addition salt thereof or an  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  protected derivative thereof which comprises (a) reacting a cyclohexanone of general formula II

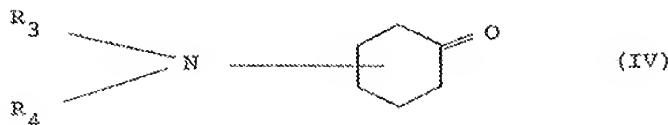


(wherein  $R_3$  and  $R_4$  are as defined above or a protected  $R_3$  or  $R_4$  derivative thereof and

X represents a nucleophilic leaving group with a thiourea of general formula III

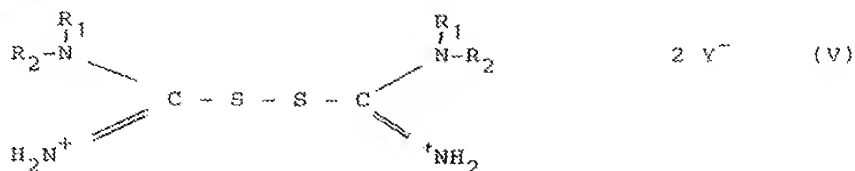


wherein  $R_1$  and  $R_2$  are as defined above or a protected  $R_1$  or  $R_2$  derivative thereof; or (b) reacting a compound of general formula IV

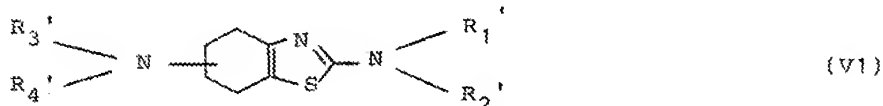


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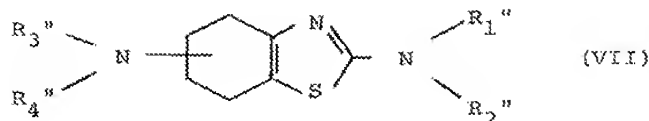
wherein  $R_3$  and  $R_4$  are as defined above or a protected  $R_3^-$  or  $R_4^-$  derivative thereof with a formamidine disulphide of general formula V



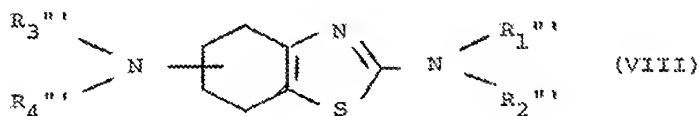
wherein  $R_1$  and  $R_2$  are as defined above or a protecting group thereof and  $Y^-$  represents an anion of an inorganic or organic acid; or (c) to prepare a compound of general formula I wherein at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents a hydrogen atom, cleaving a protecting group from a compound of general formula VI



(wherein at least one of the groups  $R_1'$ ,  $R_2'$ ,  $R_3'$  or  $R_4'$  represent a protecting group for an amino group, or  $R_1'$  and  $R_2'$  or  $R_3'$  and  $R_4'$  together with the nitrogen atom between them represent an imido group; and the remaining groups  $R_1'$ ,  $R_2'$ ,  $R_3'$  and  $R_4'$  have the meanings given for  $R_1$  to  $R_4$  above other than acyl groups); or (d) to prepare a compound of general formula I wherein at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents an alkyl or phenylalkyl group reducing a compound of general formula VII



(wherein at least one of the groups  $R_1''$ ,  $R_2''$ ,  $R_3''$  or  $R_4''$  represents one of the acyl or phenylacyl groups mentioned above; and the remaining groups have the meanings given respectively for  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  above with a metal hydride in the presence of a solvent; or (e) to prepare a compound of general formula I wherein at least one of the groups  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  represents an alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group reacting a compound of general formula VIII



(wherein  $R_1'''$ ,  $R_2'''$ ,  $R_3'''$  and  $R_4'''$  are as defined above for  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  respectively with the proviso that at least one of  $R_1'''$ ,  $R_2'''$ ,  $R_3'''$  and  $R_4'''$  represents a hydrogen atom) with a compound of general formula IX



(wherein  $R_5$  represents an appropriate alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl group; and Z represents a nucleophilic

leaving group; or Z together with an adjacent hydrogen of the group  $R_5$  represents an oxygen atom); and if required deprotecting any of the radicals  $R_1$ ,  $R_2$ ,  $R_3$ , or  $R_4$ ; and if required converting a compound of formula I thus obtained wherein at least one of the groups  $R_1$  and  $R_3$  represents a hydrogen atom, by a suitable acylation into a corresponding compound of general formula I wherein at least one of groups  $R_1$  and  $R_3$  represents one of the acyl groups mentioned above; and if required converting a compound of general formula I initially obtained further into an acid addition salt thereof or converting an acid addition salt of a compound of general formula I initially obtained into a compound of general formula I.

2. A process as claimed in claim 1(a) wherein in the compound of formula II X represents a halogen atom.
3. A process as claimed in claim 2 wherein in the compound of formula II X represents a chlorine or bromine atom.
4. A process as claimed in claim 1(c) wherein in the compound of formula V at least one of the groups  $R'_1$ ,  $R'_2$ ,  $R'_3$  or  $R'_4$  represents an acyl or alkoxycarbonyl group.
5. A process as claimed in claim 1(c) wherein in the compound of formula V at least one of the groups  $R'_1$ ,  $R'_2$ ,  $R'_3$  or  $R'_4$  represents an acetyl, propionyl, methoxycarbonyl or ethoxycarbonyl group.

A



6. A process as claimed in claim 1(e) wherein in the compound of formula IX Z represents a halogen atom or a sulphonic acid group.
7. A process as claimed in claim 1(e) ~~or f~~ wherein in the compound of formula IX Z represents a chlorine, bromine or iodine atom or a methoxysulphonyloxy or p-toluenesulphonyloxy group.
8. A process as claimed in claim 1 wherein the reaction is carried out in the presence of a solvent.
9. A process as claimed in claim 1(a), 2 or 3 wherein the reaction is carried out at a temperature of between 0 and 150°C.
10. A process as claimed in claim 1(a) , 2 or 3 wherein the reaction is carried out at a temperature of between 20 and 100°C.
11. A process as claimed in claim 1(b) wherein the reaction is carried out at a temperature of between 50 and 200°C.
12. A process as claimed in claim 1(b) wherein the reaction is carried out at a temperature of between 70 and 150°C.
13. A process as claimed in claim 1(c), 4 or 5 wherein the cleavage of a protecting group is carried out by hydrolysis in the presence of a base or acid.

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14. A process as claimed in claim 1(c), 4 or 5 wherein the reaction is carried out at a temperature of between 50 and 150°C.
15. A process as claimed in claim 1(c), 4 or 5 wherein the cleavage of a protecting group is carried out by hydrolysis in the presence of a base or acid at a temperature of between 50 and 150°C.
16. A process as claimed in claim 1(d) wherein the reduction is carried out with lithium aluminum hydride.
17. A process as claimed in claim 1(d) or 16 wherein the reduction is carried out at a temperature of between 0 and 100°C.
18. A process as claimed in claim 1(d) or 16 wherein the reduction is carried out at a temperature of between 20 and 80°C.
19. A process as claimed in claim 1(e), 6 or 7 wherein Z represents a nucleophilic leaving group and the reaction is carried out at a temperature of between -10 and 50°C.
20. A process as claimed in claim 1(e), 6 or 7 wherein Z represents a nucleophilic leaving group and the reaction is carried out at a temperature of between 0 and 30°C.
21. A process as claimed in claim 1(e), 6 or 7 wherein Z represents a nucleophilic leaving group and the reaction is carried out in the presence of a base at a temperature of between -10 and 50°C.

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A.

22. A process as claimed in claim 1(e), 6 or 7 wherein Z represents a nucleophilic leaving group and the reaction is carried out in the presence of a base at a temperature of between 0 and 30°C.

23. A process as claimed in claim 1(e), 6 or 7 wherein, the reaction is carried out with a carbonyl compound of general formula IX as defined in claim 1 in the presence of a complex metal hydride at a temperature of between 0 and 50°C.

24. A process as claimed in claim 1(e), 6 or 7 wherein, the reaction is carried out with a carbonyl compound of general formula IX as defined in claim 1 and the reduction is carried out at ambient temperature.

25. A process as claimed in claim 1(e), 6 or 7 wherein the reaction is carried out with a carbonyl compound of general formula IX as defined in claim 1, in the presence of sodium borohydride or sodium cyanoborohydride at a temperature of between 0 and 50°C.

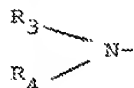
26. A process as claimed in claim 1(e), 6 or 7 wherein, the reaction is carried out with a carbonyl compound of general formula IX as defined in claim 1, in the presence of sodium borohydride or sodium cyanoborohydride at ambient temperature.

27. A process as claimed in claim 1 wherein a compound of formula I as defined in claim 1 thus obtained which contains at least one chiral centre is resolved into its enantiomers.

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28. A process as claimed in claim 1 wherein a compound of formula VI, VII or VIII is obtained by a process of claim 1(a) or 1(b).

29. A process as claimed in claim 1 wherein the



group is in the 5 or 6-position.

30. A process as claimed in claim 1

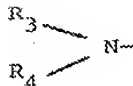
(wherein the group  $\begin{array}{c} R_3 \\ \diagdown \\ N- \\ \diagup \\ R_4 \end{array}$  occupies the 5 or 6-position and

$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichlorobenzyl or phenylethyl group;

$R_2$  represents a hydrogen atom or a methyl or ethyl group; and

$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms or an allyl, propargyl, benzyl, chloro-benzyl, phenylethyl, cyclopentyl or cyclohexyl group, and  $R_4$  represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl group; or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group).

31. A process as claimed in claim 30, wherein the



group is in the 6-position.

32. A process as claimed in claim 30 or 31  
(wherein

$R_1$  and  $R_2$  together with the nitrogen atom between them represent an amino or allylamino group and

$R_3$  and  $R_4$  together with the nitrogen atom between them represent a dimethylamino, diethylamino, N-allyl-N-(4-chlorobenzyl)-amino, n-propylamino or pyrrolidino group).

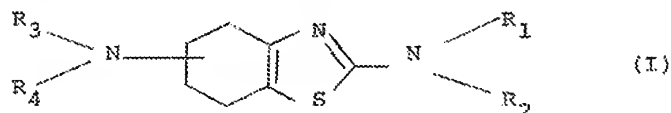
33. A process as claimed in claim 1 wherein  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  each represent methyl and the dimethylamino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  together with the nitrogen atom represent pyrrolidino and the pyrrolidino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen, one of  $R_3$  and  $R_4$  represents n-propyl, the other represents hydrogen and the n-propylamino group is in the 6-position; or one of  $R_1$  and  $R_2$  represents allyl, the other represents hydrogen,  $R_3$  and  $R_4$  each represent methyl and the dimethylamino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen, one of  $R_3$  and  $R_4$  represents allyl, the other represents 4-chlorobenzyl and the N-allyl-N-(4-chlorobenzyl)-amino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  each represent allyl and the diallylamino group is in the 6-position.

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34. A process as claimed in claim 1 wherein the compound of formula I as defined in claim 1 is recovered in the form of a pharmaceutically acceptable acid addition salt thereof or is converted into a pharmaceutically acceptable acid addition salt thereof.

35. A process as claimed in claim 34 wherein the acid addition salt is formed with hydrochloric, hydrobromic, sulphuric, phosphoric, lactic, citric, tartaric, succinic, maleic or fumaric acid.

36. A compound of general formula I



[wherein

$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 6 carbon atoms in the alkyl part or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or 2 halogen atoms);

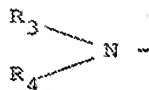
$R_2$  represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms; and

$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 7 carbon atoms, a cycloalkyl group containing 3 to 7

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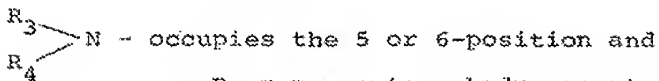
carbon atoms, an alkenyl or alkynyl group each containing 3 to 6 carbon atoms or an alkanoyl group containing 1 to 7 carbon atoms in the alkyl part or represents a phenylalkyl or phenylalkanoyl group each containing 1 to 3 carbon atoms in the alkyl part (in which the phenyl nuclei may be substituted by 1 or more fluorine, chlorine or bromine atoms), and  $R_4$  represents a hydrogen atom, an alkyl group containing 1 to 4 carbon atoms or an alkenyl or alkynyl group each containing 3 to 6 carbon atoms, or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group] or an acid addition salt thereof,

37. A compound according to claim 36 wherein the



group is in the 5 or 6-position.

38. A compound according to claim 36 wherein the group



$R_1$  represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl, benzyl, 2-chloro-benzyl, 4-chloro-benzyl, 3,4-dichlorobenzyl or phenylethyl group;

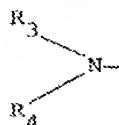
$R_2$  represents a hydrogen atom or a methyl or ethyl group; and

$R_3$  represents a hydrogen atom, an alkyl group containing 1 to 6 carbon atoms or an allyl, propargyl, benzyl, chloro-benzyl, phenylethyl, cyclopentyl or cyclohexyl group, and  $R_4$

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represents a hydrogen atom, an alkyl group containing 1 to 3 carbon atoms or an allyl group; or  $R_3$  and  $R_4$  together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group.

39. A compound according to claim 38 wherein the



group is in the 6-position.

C 40. A compound according to claim 38 ~~or 39~~ wherein

$R_1$  and  $R_2$  together with the nitrogen atom between them represent an amino or allylamino group and

$R_3$  and  $R_4$  together with the nitrogen atom between them represent a dimethylamino, diethylamino, N-allyl-N-(4-chlorobenzyl)-amino, n-propylamino or pyrrolidino group.

41. A compound according to claim 36 wherein  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  each represent methyl and the dimethylamino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  together with the nitrogen atom represent pyrrolidino and the pyrrolidino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen, one of  $R_3$  and  $R_4$  represents n-propyl, the other represents hydrogen and the n-propylamino group is in the 6-position; or one of  $R_1$  and  $R_2$  represents allyl, the other represents hydrogen,  $R_3$  and  $R_4$  each represent methyl and the dimethylamino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen, one of  $R_3$  and  $R_4$  represents

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allyl, the other represents 4-chlorobenzyl and the N-allyl-N-(4-chlorobenzyl)-amino group is in the 6-position; or  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  each represent allyl and the diallylamino group is in the 6-position.

42. A pharmaceutically acceptable acid addition salt of a compound of formula I as defined in claim 36.

43. A compound according to claim 36 wherein  $R_1$  and  $R_2$  each represent hydrogen,  $R_3$  and  $R_4$  each represent methyl and the dimethylamino group is in the 6-position.

44. A process for preparing 2-amino-6-dimethylamino-4, 5, 6, 7-tetrahydro-benzthiazole or the dihydrochloride salt thereof which process comprises brominating 4-dimethylamino-cyclohexanone and reacting the  $\alpha$ -bromo-4-dimethylamino-cyclohexanone obtained with thiourea and, if required, converting the final product obtained into the dihydrochloride salt thereof.

45. A process for preparing 2-amino-6-dimethylamino-4, 5, 6, 7-tetrahydro-benzthiazole which process comprises reacting 4-dimethylamino-cyclohexanone with formamidine-disulphide-dihydrobromide.

46. 2-Amino-6-dimethylamino-4,5,6,7-tetrahydro-benzthiazole or the dihydrochloride salt thereof.

47. A compound according to claim 36 wherein  $R_1$  and  $R_2$  each represent hydrogen, one of  $R_3$  and  $R_4$  is hydrogen, the other is n-propyl and the n-propylamino group is in the 6-position.

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48. A process for preparing 2-amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole or the dihydrochloride salt thereof which process comprises reacting 2,6-diamino-4,5,6,7-tetrahydrobenzthiazole with n-propanol and if required converting the product obtained into the dihydrochloride salt thereof.

49. A process as claimed in claim 48 wherein the 2,6-diamino-4,5,6,7-tetrahydro-benzthiazole is obtained by treating 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole with hydrazine hydrate to remove the protecting group.

50. A process as claimed in claim 49 wherein the 2-amino-6-phthalimido-4,5,6,7-tetrahydro-benzthiazole is obtained by brominating 4-(phthalimido)-cyclohexanone and reacting the  $\alpha$ -bromo-4-(phthalimido)-cyclohexanone with thiourea.

51. 2-Amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole or the dihydrochloride salt thereof.

52. (-)-2-amino-6-n-propylamino-4,5,6,7-tetrahydro-benzthiazole or the dihydrochloride salt thereof.

53. A pharmaceutical composition comprising a compound according to claim 36 as the active ingredient in association with a pharmaceutically acceptable carrier or excipient.

54. A pharmaceutical composition according to claim 53 in the form of a tablet, powder, suppository, suspension, droplet, or ampoule.
55. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 37.
56. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 38.
57. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 39.
58. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 40.
59. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 41.
60. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 42.
61. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 43.
62. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 46.

63. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 51.

64. A pharmaceutical composition according to claim 53 or 54 wherein the active ingredient is according to claim 51.

65. A composition according to claim 53 in unit dosage form.

66. A composition according to claim 65 wherein said unit dose comprises 0.01 to 0.5 mg/kg body weight of the active ingredient.

67. A composition according to claim 65 wherein said unit dose comprises 0.1 to 3 mg/kg body weight of the active ingredient.

68. A process for preparing a pharmaceutical composition comprising a compound as defined in claim 36 as the active ingredient which process comprises admixing said active ingredient with a pharmaceutically acceptable carrier or excipient.

69. The use of a compound according to claim 36, 37 or 38 to ameliorate a central nervous or circulatory disorder.

70. The use of a compound according to claim 39, 40 or 41 to ameliorate a central nervous or circulatory disorder.

71. The use of a compound according to claim 42 to ameliorate a central nervous or circulatory disorder.
72. The use of a compound according to claim 43 or 46 to ameliorate a central nervous or circulatory disorder.
73. The use of a compound according to claim 47 or 51 to ameliorate a central nervous or circulatory disorder.
74. The use of a compound according to claim 52 to ameliorate a central nervous or circulatory disorder.

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PATENT AGENTS



**SUBSTITUTE**

***REMPLACEMENT***

**SECTION is not Present**

***Cette Section est Absente***